Remarks

The status of the claims is as follows:

Active: claims 28, 30-37, and 39-43;
Active and Independent: claims 28 and 37;
Withdrawn: claims 16-18 and 21-23; and
Canceled: claims 1-15, 19, 20 and 24-27, 29 and 38, without prejudice or disclaimer.

Support for amending claims 28 and 37 (and withdrawn claim 16) to recite that the ratio of excipient to methylcobalamin is from 2.5 to 25 parts by weight, based on 1 part by weight of methylcobalamin, is found, *inter alia*, at specification page 11, lines 6-9.

Support for amending claims 28 and 37 to recite that the sugar that is present in the amorphous state is present in the excipient in an amount that is at least 20% by weight, based on the total weight of said excipient, is found, *inter alia*, in canceled claims 29 and 38, respectively.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Error in the Translation of Miyake

As the previous interview with the Examiner, Applicants discussed that there appeared to be a error in the translation of the Miyake document (JP 63-313736; herein

"Miyake") that was provided by the Office. Specifically, the last sentence of the Office's translation of Miyake was believed to be incorrect.

The last sentence in the Office's translation reads:

> We carried out the same operations as Practical Example 1 except that we added propylene glycol and we obtained a comparative control product.

Applicants have examined the original Japanese language document. The last sentence in Miyake should read:

> We carried out the same operations as Practical Example 1 except that we **did not add** propylene glycol and we obtained a comparative control product. (emphasis added)

The Office is encouraged to correct its translation.

The Advisory Action

In the Advisory Action, claims 28-43 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Miyake *et al.*, (JP 63-313736; herein "Miyake") in view of Driskell, Sports Nutrition, CRC Press, page 75, (2000) (herein "Driskell"). Miyake is relied on as disclosing a preparation containing vitamin B_{12}, lactose, an antioxidant, and a pH adjuster which is then freeze-dried. Driskell is relied on as evidence that methylcobalamin is the active form of B_{12}. Applicants respectfully traverse this rejection and respectfully request reconsideration.

The claims have been amended to recite that the ratio of the excipient to methylcobalamin is from 2.5 to 25 parts by weight, based on 1 part by weight of

methylcobalamin. In contrast, Miyake describes a freeze-dried preparation in which 50 mg of lactose is present with respect to 10 μg of cyanocobalamin. In other words, in Miyake, the excipient, lactose, is present at a ratio of 5000 parts by weight, based on 1 part by weight of cyanocobalamin. The ratio of lactose/excipient to cyanocobalamin in Miyake's composition is 200 times that of the composition of the invention as currently claimed.

Although Examiner asserts in the advisory action that the compositions of Miyake and those of Applicants are substantially identical, Applicants respectfully disagree, for reasons already of record. In addition, by the current amendment, the claimed composition and the prior art composition are even more distinguished and even more clearly not substantially identical.

There is no evidence that the skilled artisan would have been motivated to formulate the vitamin formulation of Miyake with such a low amount of lactose, much less formulate the claimed methylcobalamin composition of the invention.

As previously discussed, Applicants respectfully maintain that the closest prior art composition in Miyake to Applicants' generic claim is the composition that lacks the polyhydric alcohol. Miyake's composition that contained lactose but that lacked a polyhydric alcohol possessed negative properties that made it undesirable for use even with cyanocobalamin, much less desirable for use with the a unstable compound such as methylcobalamin. There was no suggestion that lowering the lactose in the control composition would result in a composition that could stabilize a different compound,

methylcobalamin. Thus, the art taught away from pursuing the direction that Applicants took in reaching their invention.

The same conclusion is reached if one compares Applicants' claimed composition with Miyake's composition that contained polyhydric alcohol. There is no suggestion that lowering the ratio of lactose/excipient to cyanocobalamin would provide any advantage with regard to a different compound that was more unstable in long term freeze-dried storage.

Additionally, Applicants provided evidence of unexpected results in two respects. First, Applicants demonstrated surprising results in the ability of the claimed composition to provide for the long term storage stability of freeze-dried preparation and/or high temperature stability of the freeze-dried methylcobalamin preparations (see for example, page 16, (lines 13-16) and Figures 9-12 and also see page 24 (lines 19-22).

Second, Applicants demonstrated surprising results with regard to the discovery that the presence of an amorphous excipient stabilized freeze-dried methylcobalamin against degradation. For example, see specification page 27 where it is stated that Applicants' results show that methylcobalamin is more unstable in a crystalline environment than in a non-crystalline environment. Such results are contrary to the understanding in the art, as evidenced, for example, by Craig et al., J. Pharmaceut. 179: 179-207 (1999) (herein "Craig"), cited by the Examiner in the Office action dated July 22, 2009 that states:

> Given the potential advantages of preparing drugs in an amorphous form, the question arises as to why this approach is not used more often. **The single most important**

> **reason is undoubtedly the problems associated with stability, both physical and chemical**. The amorphous state is, by definition, metastable with regard to the crystalline material, hence amorphous drugs will tend to revert to the crystalline form over a period of time. Prediction of the timescales involved is clearly critical and yet may be difficult to achieve.

Craig, pp. 193-194 (emphasis added).

Also, at Craig page 196, column 2, section 3.3 it is stated:

> Numerous reports have shown that rates of drug degradation may be enhanced in the amorphous state compared to the crystalline material.

Also, as discussed in the reply to the 7/22/2009 Office action, Roberts *et al.*, AIChE Journal 48: 1140 (June 2002), (document NPL22 in the Fourth Supplemental IDS filed November 20, 2009), at page 1143, first column, last paragraph, state:

> "The quantitative prediction of storage stability is thus not possible at the present. Understanding the dynamics of structural relaxation of the glassy matrix on the time scale of years is also a challenging problem, and one in which progress must be made before storage stability can be reliably estimated and engineered."

Thus, the art acknowledges that the quantitative prediction of storage stability is not possible in 2002 when Roberts published, and that engineering of long term stability was unreliable.

The result achieved by the claimed invention was not reasonably predictable based on Miyake in view of Driskell. The evidence of record, and above, establishes that the invention, even if characterized as a combination of familiar elements, yields more than predictable results. That is, the invention is more than the predictable use of the prior elements according to their established functions. The invention is more than a simply substitution of one known element for another to obtain a predictable result. Thus, the invention is therefor non-obvious.

As to solving the problem of the chemical instability of methylcobalamin in long term freeze-dried storage, there were not a finite number of identified, predictable solutions. The possible options for stabilizing freeze-dried methylcobalamin, especially chemically stabilizing the freeze-dried compound, were unknown in view of the art. There is no suggestion that the presence of an excipient that is in an amorphous form could stabilize the chemical structure of a different compound, freeze-dried methylcobalamin. The long term stability achieved by the claimed invention is unexpected in view of the knowledge in the art.

The discussion above has shown that the rational underpinnings that are the basis of Examiner's articulated reasoning do not ground a conclusion of obviousness Therefore, Applicants respectfully assert that a *prima facie* case of obviousness of the claimed invention is not established, or if it has been established, it has been overcome.

Conclusion

Prompt and favorable consideration of this Reply is respectfully requested. All of the stated grounds of objection and rejection have been properly traversed,

accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Michele A. Cimbala
Attorney for Applicants
Registration No. 33,851

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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